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Clinical Characteristics and Outcome of Klebsiella Pneumonae Sepsis in Neonates

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ABSTRACT

Background: Klebsiella Pneumonae is one of the most frequent isolates in blood cultures for neonatal sepsis. Of special concern, are the varied mortality rates and sensitivity patterns in different studies done from the same region or country. **Objective:** This study was conducted to define the frequency, clinical and laboratory profiles of Klebsiella Pneumonae sepsis cases in our neonatal intensive care unit at Fatima Memorial Hospital, Lahore. **Study Design:** Retrospective cross-sectional study. **Settings:** Neonatal Intensive care unit at Fatima Memorial Hospital (FMH), Lahore Pakistan. **Duration:** 1st-Jan-2019 to 31st Dec 2020. **Methods:** A retrospective analysis of blood culture result data was done for 2 years from Jan 2019 to Dec 2020. The clinical records of the babies with Klebsiella positive in their blood culture were accessed for the epidemiological, clinical and laboratory data, and analysed with SPSS 21. **Results:** A total of 28 cases, 26 with Klebsiella Pneumonae and one each with Klebsiella oxytoca and non-specific klebsiella, were included in the study. The incidence was 58.3% (28 out of total 48 positive blood cultures). The mean gestation was 34.9 ± 3.8 weeks, and the mean weight was 2.45 ± 0.96 kg. Most were male (64.3%) and delivered via C-section (60.7%). Most of the babies were referred to us (75%) and 64.3% had klebsiella Pneumonae growth at the time of admission to our unit. Most cases were Late-onset sepsis (24 out of 28). The maximum sensitivity was to colomycin (71.4%) and then to meropenem (50%). There was about 60% resistance to aminoglycosides, ciprofloxacin, imipenem, tazobactam-piperacillin and co-trimoxazole. The 3rd generation cephalosporins had poor sensitivity of 3.5-17.8%. The mortality was 39.3% (11 out of 28), which was significantly associated with prematurity (<32 weeks), low birth weight (<1500gm), referred cases (out-born), hospital acquired infection, use of mechanical ventilation, and the use of long lines and TPN. **Conclusion:** Klebsiella sepsis is the commonest cause of neonatal sepsis with high mortality. It is common in preterms and low birth weight babies, referral of babies, mechanical ventilation, use of long lines and TPN. Carbapenem resistance is 50-60%, thus limiting antibiotic choices.

Keywords: Neonatal sepsis, Klebsiella sepsis, Klebsiella pneumonae, Neonatal mortality, Multi-drug resistance, Carbapenem-resistant.

INTRODUCTION

Neonatal sepsis varies greatly across hospitals, communities, countries and even regions, ranging from 7.1 to 38 (per 1000 live births) in Asia, 6.5 to 23 in Africa and 2 to 4 in developed nations. Pakistan has one of the highest neonatal mortality rates (41.2 per 1000 live births) in the world. Of the many, neonatal sepsis is the 2nd most common cause in 2019.[1,2] Sepsis is directly associated with many co-morbid conditions such as white matter injury and bronchopulmonary dysplasia, further adding to the mortality. Many factors, at different levels, contribute to these dismal figures such as poor finances, poor prevention strategies, limited diagnostic as well as treatment facilities, highly susceptible population, shortage of trained staff, early colonization, and indiscriminate use of antibiotics.

Neonatal sepsis can be divided into Early-onset sepsis (EOS), which is sepsis occurring within the first 72 h of

life, and the Late onset type, which happens after 72 hours of life.[3]

Klebsiella Pneumonae is the commonest bacterial isolate from blood cultures from neonatal intensive care units (NICU). Its incidence varies from 17% in India and 37% in Pakistan, with variable mortality of 18-68%.[4,5,6] High mortality is associated with Klebsiella sepsis. The high mortality is directly linked to the emergence of multi-drug resistant strains. Multidrug-resistant (MDR) strains were defined as per international standard definitions for acquired resistance and relative to the panel of antibiotics tested for each isolate, as in vitro non-susceptibility to ≥1 agent in ≥3 antimicrobial categories: Penicillins, Cephalosporins, Beta-lactamase inhibitor combinations, Fluoroquinolones, Aminoglycosides, Chloramphenicol, Folate pathway inhibitors, Tetracyclines, Macrolides and Glycopeptides.[7,8] Especially concerning are the reports of carbapenem-resistant Klebsiella Pneumonae outbreaks, both from hospitals and communities.[9]

This study was conducted to define the frequency, clinical and laboratory profile of Klebsiella Pneumonae sepsis in our neonatal intensive care unit at Fatima Memorial Hospital, Lahore.

METHODS

We did a retrospective cross-sectional study in our Neonatal Intensive care unit at Fatima Memorial Hospital (FMH), Lahore (Pakistan) from 1st-Jan-2019 to 31st Dec 2020. The babies who had positive blood cultures for Klebsiella Pneumonae were included in this study.

We admit babies in NICU who are either born in FMH (in-born) or referred to us from other hospitals. Blood cultures are requested for all babies with suspicion of sepsis, at the time of admission. Neonates would present with varied signs of sepsis, such as temperature instability, feeding difficulties, respiratory distress or apneas, hemodynamic instability, prolonged need for intravenous fluids, convulsion, hypotonia or irritability. The presence of prolonged rupture of membranes for >18 hours or signs of maternal chorioamnionitis are also considered risk factors for sepsis. Repeat blood cultures are also requested depending on clinical condition of the baby.

The blood cultures are drawn by a doctor or a senior nurse with a strict aseptic protocol. Two disinfectants are used - 10% Povidone-iodine solution followed by an alcohol swab. One to two millilitres of blood is added to BACTEC PedsPlus™ (Becton Dickinson, Ireland) culture vials and processed for 5 days in an automated BACTEC system. Standard procedures are followed for bacterial culture, identification and antibiotic testing.[10]

Microbiology data was reviewed for Klebsiella Pneumonae positive blood culture results. The records of these babies were then assessed for the data such as age at admission, gestational age, birth weight, maternal factors, clinical signs, laboratory parameters, and antibiotic susceptibility patterns.

Statistical Package for Social Sciences (SPSS) version 21 was used for data entry and analysis. Categorical variables were expressed as frequency and percentages, whereas continuous variables were expressed as mean with standard deviation. A p-value of less than 0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Review Board of FMH.

RESULTS

During the study period of 2 years, there were 8881 total admissions to the neonatal unit, of which, 2326 babies were admitted to the NICU. Of these, 48 (0.54% of total and 2% of NICU admissions) babies had positive blood cultures for various bacteria. Klebsiella was the commonest isolated pathogen (28 out of 48 - 58.3%) during these 2 years. Of 28 positive cases, 26 were Klebsiella Pneumonae, one non-specific klebsiella and one Klebsiella oxytoca. We are, however, presenting data for all 28 cases.

The demographic data of the cases are shown in Table 1. The mean gestation was 34.9 ± 3.8 weeks, and the mean weight was 2.45 ± 0.96 kg. Most were male (64.3%) and delivered via C-section (60.7%). Most of the babies were referred to us (75%) and 64.3% had klebsiella Pneumonae growth at the time of admission to our unit. Most were Late-onset sepsis (24) but surprisingly 4 babies had klebsiella sepsis within 1st 3 days of life.

A total of 11 babies expired with 39.3% mortality. Mortality was significantly associated with gestational age (p-Value 0.004, higher risk in prematurity, <32 weeks), birth weight (p-value 0.01, smaller the baby higher the mortality risk), referred cases (out-born p-Value 0.04) and hospital-acquired infection (later/repeat cultures p-Value 0.013).

The clinical and Lab data are shown in Table 2. History of prolonged rupture of membranes was present only in 6 cases, 5 cases had a history of long line insertion and TPN usage. Thirteen babies had a history of previous invasive ventilation. The Klebsiella sepsis resulted in 18 babies requiring or extending mechanical ventilation with a mean of 7.4 ± 9.8 days and a prolonged duration of NICU (mean 7.4 ± 6.6 days). Of the lab parameters, the mean C-Reactive Protein was 85.6 + 74.2, White cell count 18.7 + 9.7 and platelet count 124.5 + 110.

Of note, mortality was significant with the use of long lines (p-value 0.04) and TPN (p-Value 0.04). The presence

of thrombocytopenia was marginally significant (p-Value 0.06).

The sensitivity pattern of our Klebsiella isolates have been as shown in the graph:

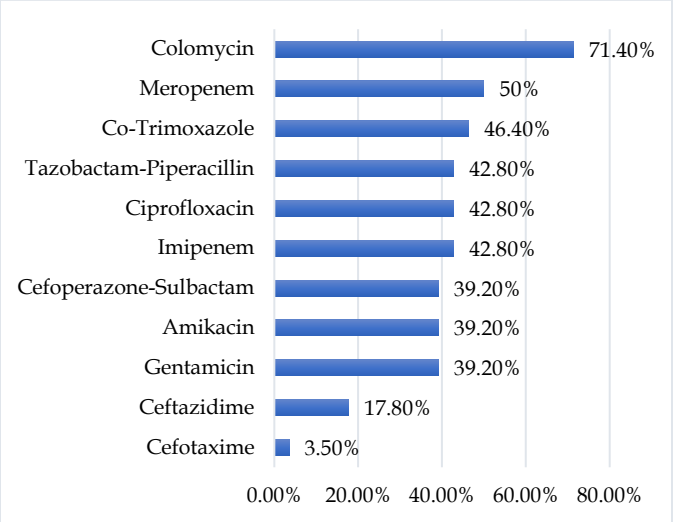
Table 1: Demographic Data

Variable	Category	Number Total 28 (%)	Mortality – Number (%)	p-Value
Gestation at Birth Mean – 34.9 ± 3.8	<28 weeks	1 (3.6%)	1 (100%)	**0.004**
	28-32 weeks	5 (17.9%)	4 (80%)	
	32 ± 37 weeks	11 (39.3%)	6 (54.5%)	
	>37 weeks	11 (39.3%)	0	
Birth Weight Mean – 2.45 ± 0.96	<1kg	2 (7.1%)	2 (100%)	**0.01**
	1-1.5kg	3 (10.7%)	3 (100%)	
	1.51-2kg	6 (21.4%)	3 (50%)	
	2.1-3kg	9 (32.1%)	3 (33.3%)	
	>3kg	8 (28.6%)	0 (0)	
Gender	Male	18 (64.3%)	9 (50%)	0.119
	Female	10 (35.7%)	2 (25%)	
Mode of Delivery	SVD	11 (39.3%)	6 (54.5%)	0.184
	C-Section	17 (60.7%)	5 (29.4%)	
Place of Birth	In-Born – FMH	7 (25%)	5 (71.4%)	0.044
	Out Born	21 (75%)	6 (28.5%)	
Type of Sepsis	EOS	4 (14.3%)	1 (25%)	0.52
	LOS	24 (85.7%)	10 (41.7%)	
Time of CS	At admission	18 (64.3%)	4 (22.2%)	0.013
	Later	10 (35.7%)	7 (70%)	

Table 2: Clinical Data

Variable Name	Category	Number (%)	Mortality Number (%)	p-Value
Maternal Risk Factors	Yes	6 (21.4%)	4 (66.7%)	0.12
	No	22 (78.6%)	7 (31.8%)	
Previous Assisted Ventilation	Yes	13 (46.4%)	10 (76.9%)	**0.00**
	No	15 (53.6%)	1 (6.7%)	
Use of Long Lines	Yes	5 (17.9%)	4 (80%)	**0.04**
	No	23 (82.1%)	7 (30.4%)	
Use of TPN	Yes	5 (17.9%)	4 (80%)	**0.04**
	No	23 (82.1%)	7 (30.4%)	
C-Reactive Protein Mean – 85.6 ± 74.2	Yes	22 (78.6%)	9 (40.9%)	0.74
	No	6 (21.4%)	2 (33.3%)	
White Cell Count Mean – 18.7 ± 9.7	Yes	19 (67.9%)	8 (42.1%)	0.66
	No	9 (32.1%)	3 (33.3%)	
Platelets Mean 124.5 ± 110	Low Count - Yes	17 (60.7%)	9 (52.9%)	0.06
	Normal Count	11 (39.3%)	2 (18.2%)	
Need for Invasive Mechanical Ventilation	Yes	18 (64.3%)	10 (55.6%)	0.18
	No	10 (35.7%)	1 (10%)	

Figure 1: Sensitivity pattern for klebsiella



The highest sensitivity was with colomycin (71.4%), followed by meropenem (50%). Of all, 3rd generation cephalosporins fared poorly. The meropenem-sensitivity had no correlation with mortality (p value 0.39).

DISCUSSION

Klebsiella Pneumoane is one of the commonest pathogens isolated from neonatal blood cultures all over the world. In other studies from Pakistan, Klebsiella was found in 3.7% of all admitted cases in Karachi and 36.5% of all positive cultures in Bahawalpur.[4,6] Our unit has, fortunately, a lower number, i.e., 0.32% of total and 1.2% of NICU admissions. When considering prevalence in positive cultures, we had klebsiella in 58.3% of cases, higher than in a study from Bahawalpur.[4] In a study from an Arab region, it was the commonest isolate in Iraq (31%), Egypt (33%), and 49% of Jordan. But it ranked lower in other countries in the region such as Saudi Arabia, Libya and the United Arab Emirates.[12] In Nepal, the frequency was 7.7-33.3%, in Ethiopia 34.3% and India varied from 17-40%.[7,13,14] We have a lesser number of klebsiella, but it was the commonest of all bacteria. It is significant, because our unit is a referral unit, with most babies (75% had blood culture sent at the time of admission) with klebsiella, being referred to us from other hospitals.

Low birth weight (<1500gms) and premature babies are especially prone to mortality in klebsiella sepsis.[5,6] Our study shows a similar and clinically significant pattern with smaller (<1500gm) and premature (<32weeks) babies. Moreover, referred babies as well as babies staying for the long in NICU resulting in hospital acquired infections are additional risk factors. Of the clinical characteristics, three prominent risk factors for mortality in K. Pneumonae sepsis are the history of previous use of mechanical ventilation, use of long lines and total parenteral nutrition. In the published literature regarding klebsiella sepsis, mechanical ventilation, low birth weight (<1500gm), duration of hospital stay of >15 days, and use of total parenteral nutrition had been significant risk factors.[5]

About 70% of our Klebsiella isolates were sensitive to colomycin, which belongs to the polymixin class, and is increasingly being used for many multi-drug resistant bacteria, especially klebsiella and acinetobacter. However, of concern, the sensitivity was not 100%, which is an alarming sign. Of the routinely used 1st line antibiotics, aminoglycosides (39.2%) fared well as compared to dismal sensitivity to 3rd generation cephalosporins (3.5-17.8%). In a study from Karachi, Pakistan, most (>80%) isolates were resistant to ampicillin + clavulanic acid, gentamicin, aztreonam, and cephalosporins. They also reported an increasing resistance to amikacin, fluoroquinolones, piperacillin/tazobactam, and imipenem was observed.[6] In a study from Nepal in 2018, sensitivities were 10% with cefotaxime, 47% amikacin, 25% gentamicin, 24% with ciprofloxacin, 88.9% with colomycin and 100% with meropenem. Our sensitivity to gentamicin and amikacin has been around 39.2%. Carbapenem resistance was 50% with meropenem and about 60% with imipenem. Thus, the available options for the treatment of multi-drug resistant Klebsiella have become limited. However, meropenem-resistance was not related to increased risk of mortality.

The reported mortality with klebsiella sepsis in neonates has been 16% in a previous study from Pakistan.[6] In our study, it is 39.3%. Our higher rate can be attributed to the larger number of referral cases from other hospitals (75%), the high-risk population (17 were premature) and growing Klebsiella at the very first blood culture (64.3% - at the time of admission). The last part is important as whenever the routine or special surveillance cultures were requested, there was no growth from the environment. In other studies, klebsiella had been isolated from incubators, suction tubes and the hands of the staff.[5]

CONCLUSION

Klebsiella Pneumonae was the most common isolated pathogen of all blood cultures in our neonates. The mortality in Klebsiella sepsis was 39.2% and was significantly associated with prematurity, low birth weight, referred cases, mechanical ventilation, and use of long lines and TPN. The mortality with Klebsiella sepsis was high but most babies were referred to us. The sensitivity to carbapenem was 40-50%.

LIMITATIONS

The study is limited by being a single center study, with short time frame.

SUGGESTIONS / RECOMMENDATIONS

Such studies done in multiple centers over multiple years may better describe K. Pneumonae sepsis clinical features and bacterial profile.

CONFLICT OF INTEREST / DISCLOSURE

None.

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